45. (New) A vector containing the nucleic acid sequence of anyone of claims 41-44, wherein said vector is capable of expressing said modified glucocorticoid receptor protein

Please cancel claim 19 without prejudice. Applicant reserves the right to pursue this subject matter in this or any other appropriate patent application. The cancellation of this claim makes no admission regarding the patentability of this subject matter and should not be so construed.

REMARKS

Applicant responds below to each of the objections and/or rejections set forth in the non-final office action mailed January 24, 2000.

1. The Election/Restriction

Claim 19 stands withdrawn from consideration from the Examiner as allegedly being drawn on a non-elected invention. In order to expedite prosecution and advance the case towards issuance, Applicant has cancelled claim 19 without prejudice.

2. The Information Disclosure Statements

The Examiner states that the Information Disclosure Statement filed December 10, 1998 fails to list all information submitted for consideration by the office and fails to provide a copy of all information listed. In order to expedite prosecution and advance the case towards issuance, Applicant has submitted a new Information Disclosure Statement herewith which lists the information to be considered by the Examiner and provides a copy of each document to be considered by the Examiner.

3. The Section 101 Rejection

Claims 13-14 and 31 stand rejected under 35 U.S.C. §101 because the claimed invention allegedly is directed to non-statutory subject matter. The Examiner states that the current recitation of "a cell" encompasses a human organism. The Examiner suggests amending the claims to recite "an isolated host cell." In order to expedite prosecution and advance the case towards issuance, Applicant has amended the claims as suggested by the Examiner. Thus, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

4. The Double Patenting Rejections

Claims 30-31 stand provisionally rejected under 35 U.S.C. §101 as allegedly claiming the same invention as that of claims 61-62 of co-pending application no. 08/479,913. In addition, claims 11-14 stand provisionally rejected under the judicially created doctrine of double patenting over claims 32, 37-49, 51-54, 56-57, and 64-66 of co-pending application no. 08/479,913. Applicant respectfully requests that the Examiner hold this matter in abeyance until the claims in this application are otherwise found allowable. Any further response at this time would be premature as the claims in one or both applications might change prior to issuance.

5. The Section 112, First Paragraph, Rejection

Claims 11-14 and 30-31 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner states that the specification is enabling for the nucleic acid encoding the modified glucocorticoid receptor protein contained within plasmid pGR0403R (i.e., from SEQ ID NO 1), but does not reasonably provide enablement for claims to any biologically functionally equivalent plasmid or DNA molecule. The Examiner argues that the current claim language sets forth no structural

characterization and little functional characteristics and encompasses any random mutation to the single disclosed nucleic acid of SEQ ID NO 1. The Examiner also argues that the specification fails to teach the particular nucleotides required for encoding the glucocorticoid receptor protein with the required activity. Indeed, the Examiner states that the skilled artisan would reasonably expect that any random modification/mutation to a nucleic acid molecule would result in an inactive encoded glucocorticoid receptor protein, citing Rudinger in support.

Applicant respectfully traverses. As an initial matter, Applicant notes that this argument appears to be inconsistent with the Examiner's obviousness argument, wherein the Examiner argues that use of equivalent constructs was well known in the art. Furthermore, Applicant notes that under 35 U.S.C. §112, first paragraph, the burden is on the Examiner to show evidence of reasons why one skilled in the art would be required to engage in undue, rather than merely routine, experimentation. One need not know beforehand with absolute certainty whether or not the claimed product, i.e., one with the desired phenotype or functional characteristic, be obtained. See *In re Angstadt and Griffin*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Here, the application describes how one skilled in the art could screen the various structural changes for functional embodiments. Given the progesterone assay, one skilled in the art could perform similar assays for other mutated receptor proteins and make other nucleic acid sequences within the scope of the claim without undue experimentation. This is manifestly true and thus it has not been shown why one skilled in the art would be unable to practice the invention without undue experimentation. This point is fully supported by the O'Malley Declaration, attached hereto as **Exhibit 1.** This declaration and its supporting exhibits convincingly demonstrates that one skilled in the art would make and use the claimed invention without undue experimentation.

The present claims are structurally limited and require use of a DNA binding domain, a transregulatory domain and a particular type of ligand binding domain. Those skilled in the art, such as Dr. O'Malley, can make and use such proteins without undue experimentation. Applicant directs the Examiner's attention to *In re Fuetterer*, 138 U.S.P.Q. 217, 223 (C.C.P.A. 1963), where Judge Rich wrote:

> We find the arguments of the board and the examiner relating to experimentation necessary to determine the suitability of *undisclosed* salts to operate in appellant's claimed combination beside the point. Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloid suspending properties. We see nothing in patent law which requires appellant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any inorganic salt which has such properties is usable in his combination. If others in the future discover what inorganic salts additional to those enumerated do have such properties, it is clear appellant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by appellant in his disclosure. The only "undue burden" which is apparent to us in the instant case is that which the Patent Office has attempted to place on the appellant. The Patent Office would require him to do research on the "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented, and is not claiming colloid suspending agents but tire tread stock composed of a combination of rubber and other ingredients.
>
> We are not persuaded that our conclusion on this point is wrong by decisions of this an other courts relating to the sufficiency of invention disclosures in cases wherein the applicant is claiming chemical *compounds* per se.

The Declaration of Dr. O'Malley is direct evidence that one skilled in the art could make and use the claimed invention.

In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

6. The Section 112, Second Paragraph, Rejection

Claims 11-12 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Examiner states that these claims are dependent on non-elected base claims.

In order to expedite prosecution and advance the case towards issuance, Applicant has amended claims 11 and 12 to place them in independent form. In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

7. The Section 102 Rejection

Claims 11-14 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Evans et al., U.S. Patent 4,981,784, or by Hollenberg et al. (1987), or by Lanz et al. (1994).

This rejection is respectfully traversed. In order for an invention to be anticipated under § 102(b), it is required that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131, *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987). Here, the rejected claims require that the modified glucocorticoid receptor protein comprise a mutated progesterone receptor ligand binding region that is capable of binding a non-natural ligand. Evans is in no way directed toward, and utterly fails to disclose the modified steroid hormone receptors of the present invention which have a mutated progesterone receptor ligand binding region that is capable of binding a non-natural ligand. In fact, Evans specifically discloses that the ligand binding domain is to be selected from the group of wild-type receptors. (Column 11, lines 30-31). Thus, the chimeric receptors of Evans comprise

ligand binding domains which exhibit the normal ligand binding activity of the receptor from which the ligand binding domain was taken. Therefore, Evans fails to disclose any LBD which is distinct from naturally occurring LBDs. Evans, therefore, fails to disclose a receptor with a mutated LBD as recited in claims 11-14. Therefore, claims 11-14 are not anticipated by Evans since Evans does not disclose every limitation recited in the claims at issue.

Hollenberg utterly fails to disclose the modified steroid hormone receptors of the present invention. The claims recite that the receptor has a mutated progesterone receptor ligand binding region that is capable of binding a non-natural ligand. Hollenberg fails to disclose any receptor which can bind dexamethasone or any other ligand, when modification is performed at the ligand-binding domain (the C-terminal). The receptors described by Hollenberg which have ligand binding activity have naturally occurring LBDs and is mutated at the DNA-binding domain, not the ligand binding domain (p. 40, col. 2, para. 4 et seq.). Hollenberg fails to disclose any mutated progesterone receptor LBDs or any receptors comprising mutated LBDs which can bind non-natural ligands. Therefore, claims 11-14 cannot be anticipated by Hollenberg because Hollenberg fails to describe a receptor that has a mutated progesterone receptor ligand binding region that is capable of binding a non-natural ligand.

The Lanz et al. paper also fails to anticipate the claimed invention. As noted above, the present claims recite a glucocorticoid receptor DNA binding domain and one or more transregulatory domains, and a mutated progesterone receptor ligand binding region capable of binding a non-natural ligand. Nothing in Lanz et al. has been shown to teach or suggest each of these limitations of the claims. Indeed, certain portions of the Lanz et al. paper appear to teach away from the present invention by describing mutations that prevent transactivation or mutations in the glucocorticoic ligand binding domain that do not allow binding of a non-natural ligand.

In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

8. The §103 Rejection

Claims 30-31 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over Hollenberg et al. or Lanz et al. The Examiner states that the Hollenberg et al. and Lanz et al. references disclose a construct pRShGRα and CS1/CD which appear to be equivalent to the pGR0403 construct of the present invention. In particular, the Examiner states that it would have been obvious to one of ordinary skill in the art at the time of filing Applicant's invention to use any vector well know in the art that can transfect the CV-1 host cells of Hollenberg or Lanz for cloning the modified glucocorticoid receptor DNA of Hollenberg or Lanz, including the same vector as used in the construction of plasmid pGR0403R because use of vectors to express equivalent DNA sequences encoding modified glucocorticoid receptors with equivalent functional activity are allegedly well known in the art and merely increase the variety of cells that this construct can successfully transform.

Applicant respectfully traverses. Claim 30 is directed to a plasmid designated as pGR0403R. This plasmid has the specific chemical structure shown in Figures 9 and 10. In order to establish a *prima facie* case of obviousness, the burden is on the Examiner to show motivation for making the specific chemical changes to the cited references required to yield the claimed plasmid. No such showing has been made and thus the rejection is improper. The general motivation alleged by the Examiner is insufficient. See, In re Deuel, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995).

In view of the above, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and requests that the application be allowed and passed to issue.

Pursuant to 37 C.F.R. §1.136, applicant hereby petitions for a two-month extension of time to take action in response to the Office Action mailed January 24, 2000. This extension of time is effective to allow timely filing of a response up to and including June 24, 2000.

A check in the amount of $190.00 is enclosed to cover the extension fee. If this fee is incorrect, please charge or credit our Deposit Account No. 12-2475 for the appropriate amount.

Respectfully submitted,

LYON & LYON LLP

Dated: 6/22/00

By: _____

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